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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,736	10/17/2003	L. K. Duncan	021123-0306247	8648

7590 06/02/2006

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,736	DUNCAN ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/9/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/17/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-6 are pending.

Applicant's election without traverse of Group I, claims 1-5 directed to a process for the production of L-lysine by culturing coryneform bacteria, in a communication filed on 3/9/2006 is acknowledged.

Claim 6 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-5 are at issue and are being examined herein.

Specification

1. The specification is objected to for the following reasons. The status of U.S. Application No. 10/078167 as shown in the preliminary amendment of 10/17/2003 has not been updated (i.e., abandoned). Appropriate correction is required.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 10/078,167 filed on 02/20/2002, and 09/531,265 filed on 03/20/2000.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 10/17/2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

4. The drawings submitted on 10/17/2003 have been reviewed and are approved by the Examiner.

Claim Rejections - 35 USC § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2 and 4 are directed to a method for the production of L-lysine wherein said method comprises cultivating L-lysine producing coryneform bacteria or corynebacteria, wherein said bacteria overexpresses by any means a genus of genes encoding 6-phosphogluconate dehydrogenases, and wherein the pyruvate oxidase activity in said bacteria is decreased or eliminated by any means. It is noted that while claim 2 adds the limitation that the overexpressed gene encoding 6-phosphogluconate is an endogenous gene, this limitation does not limit the genus of genes to be overexpressed to those found in coryneform bacteria in view of the definition of the term "endogenous" as shown in the specification (page 4, last line-page 5, line 2). The specification defines an endogenous gene as a gene which is available in the population of a species. This definition does not limit the genes to be overexpressed to those within the organism used to produce L-lysine. Claim 3 is directed to the method of claim 1 with the added limitation that overexpression of the gene is obtained by transforming the bacteria with a plasmid vector comprising the gene and a promoter. Claim 5 is directed to a method for the production of L-threonine, L-isoleucine or L-tryptophan, wherein said method comprises cultivating L-threonine, L-

isoleucine or L-tryptophan producing coryneform bacteria, wherein said bacteria overexpresses by any means a genus of genes encoding 6-phosphogluconate dehydrogenases, and wherein the pyruvate oxidase activity in said bacteria is decreased or eliminated by any means.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of nucleic acids. In addition, the claims require (1) unknown methods to increase expression of any gene encoding a 6-phosphogluconate dehydrogenase, such as transcriptional activators, or mutations within the regulatory region, and (2) unknown methods to decrease or eliminate the activity of any pyruvate oxidase in coryneform bacteria, such as mutations which would decrease/eliminate activity, or the addition of chemical/biological compounds which act as inhibitors of pyruvate oxidase activity. While the specification and/or the art disclose (1) a few 6-phosphogluconate dehydrogenases (and their corresponding coding nucleic acids) in a few organisms, (2) decrease/elimination of pyruvate oxidase activity by an insertional deletion in the *C. glutamicum* poxB

gene, and (3) increased activity of an enzyme by overexpression of a nucleic acid encoding the enzyme wherein said overexpression is the result of increasing the copy number of said nucleic acid, or using strong heterologous promoters well known in the art, the specification fails to disclose the structure of all the nucleic acids encoding 6-phosphogluconate dehydrogenases as recited in the claims, other methods to overexpress a nucleic acid encoding a 6-phosphogluconate dehydrogenase, or mutations in coryneform bacteria pyruvate oxidases which result in decreased activity, or inhibitors of coryneform bacteria pyruvate oxidases.

The claims require a genus of nucleic acids which are structurally unrelated. A sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of nucleic acids defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of nucleic acids required in the claimed invention. There is no information as to a correlation between the structures disclosed/known in the art and 6-phosphogluconate dehydrogenase activity. Furthermore, while one could argue that the structures of known nucleic acids encoding 6-phosphogluconate dehydrogenases are representative of all members of the genus of nucleic acids required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with 6-phosphogluconate

dehydrogenase activity has been provided, one cannot reasonably conclude that the known structures are representative of all the nucleic acids required in the claimed invention.

Due to the fact that the specification only discloses (1) the polynucleotide of SEQ ID NO: 2 (gene encoding a *C. glutamicum* 6-phosphogluconate dehydrogenase), (2) a single method to increase expression of a nucleic acid, and (3) a single method to decrease/inactivate pyruvate oxidase activity in *C. glutamicum*, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

7. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of L-lysine, L-threonine, L-isoleucine or L-tryptophan wherein said method comprises cultivating an L-lysine, L-threonine, L-isoleucine or L-tryptophan producing *C. glutamicum* cell which overexpresses a polynucleotide encoding the polypeptide of SEQ ID NO: 3 (*C. glutamicum* 6-phosphogluconate dehydrogenase), wherein said overexpression results from increasing the copy number of said polynucleotide, and wherein said *C. glutamicum* cell further comprises an insertional deletion in the poxB gene which inactivates pyruvate oxidase activity, does not reasonably provide enablement for a method for the production of L-lysine, L-threonine, L-isoleucine or L-tryptophan, wherein said method comprises cultivating an L-lysine, L-threonine, L-isoleucine or L-tryptophan producing coryneform bacterium or corynebacterium which comprises a polynucleotide encoding any 6-phosphogluconate dehydrogenase, wherein (1) the expression of said polynucleotide is increased by any method, and (2) the pyruvate oxidase activity of said bacterium is decreased/eliminated by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-5 are so broad as to encompass a method for the production of L-lysine, L-threonine, L-isoleucine or L-tryptophan, wherein said method comprises cultivating an L-lysine, L-threonine, L-isoleucine or L-tryptophan producing coryneform bacterium or corynebacterium which comprises a polynucleotide encoding any 6-phosphogluconate dehydrogenase, wherein (1) the expression of said polynucleotide is increased by any method, and (2) the pyruvate oxidase activity of said bacterium is decreased/eliminated by any method.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids for which there is no structure disclosed, as well as the unknown methods which would allow (1) increased expression of nucleic acids encoding 6-phosphogluconate dehydrogenases, and (2) reduction/elimination of pyruvate oxidase activity in coryneform bacteria or corynebacteria. In the instant case, the specification enables a method for the production of L-lysine, L-threonine, L-isoleucine or L-tryptophan wherein said method comprises cultivating an L-lysine, L-threonine, L-isoleucine or L-tryptophan producing *C. glutamicum* cell which overexpresses a polynucleotide encoding the polypeptide of SEQ ID NO: 3 (*C. glutamicum* 6-phosphogluconate dehydrogenase), wherein said overexpression results from increasing the copy number of said polynucleotide, and wherein said *C. glutamicum* cell further comprises an insertional deletion in the poxB gene which inactivates pyruvate oxidase activity

The amount of direction or guidance presented and the existence of working examples. The specification discloses an L-lysine *C. glutamicum* strain which overexpresses a nucleic acid encoding the polypeptide of SEQ ID NO:3 and produces L-lysine, as a working example. However, the specification fails to disclose (1) other methods to increase expression of a nucleic acid encoding a 6-phosphogluconate dehydrogenase, (2) other methods to reduce/eliminate pyruvate oxidase activity in coryneform bacteria or corynebacteria, or (3) the structure of other nucleic acids encoding 6-phosphogluconate dehydrogenases.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of a nucleic acid encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and 6-phosphogluconate dehydrogenase activity such that one of skill in the art can envision the structure of any nucleic acid encoding a 6-phosphogluconate dehydrogenase. In addition, neither the art nor the specification provide any teaching or guidance as to which structural elements in those 6-phosphogluconate dehydrogenases known in the art, or in the polypeptide of SEQ ID NO: 3, should be present in any 6-phosphogluconate dehydrogenase. The art clearly teaches the high level of unpredictability with regard to the effect of structural changes in a protein's activity when no guidance/knowledge as to which amino acids are required for activity has been provided. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski

et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for (1) all nucleic acids encoding 6-phosphogluconate dehydrogenases, (2) an essentially infinite number of mutations within the regulatory region of any gene encoding a 6-phosphogluconate dehydrogenase to obtain higher expression, (3) enhancers/activators which would increase expression of any nucleic acid encoding a 6-phosphogluconate dehydrogenase, (4) inhibitors of pyruvate oxidase activity, or (4) any mutation in pyruvate oxidases from coryneform bacteria or corynebacteria which would result in reduced or no enzymatic activity.

In the absence of (1) a correlation between structure and 6-phosphogluconate dehydrogenase activity, (2) some guidance as to the structural changes within the regulatory region of any gene encoding a 6-phosphogluconate dehydrogenase which would result in increased expression, (3) some guidance as to the structural changes required in any pyruvate oxidase from coryneform bacteria or corynebacteria to reduce or eliminate enzymatic activity, or (4) some guidance as to what is required in any compound which inhibits pyruvate oxidase activity in coryneform bacteria or corynebacteria, one of skill in the art would have to test an essentially infinite number of (1) polynucleotides to determine which ones encode 6-phosphogluconate dehydrogenases, (2) modifications within the regulatory region of a gene encoding a 6-phosphogluconate dehydrogenase to determine which ones would result in increased expression, (3) compounds/biologicals to determine which ones inhibit or eliminate pyruvate oxidase activity, and (4) enhancers/activators which would increase expression of a gene encoding a 6-phosphogluconate dehydrogenase. Therefore, taking into consideration the extremely broad scope of the claims, the lack of

guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Art of Interest

8. Mockel et al. (EP 1096013 A2 published on 5/2/2001) discloses cloning of the *C. glutamicum* poxB gene (Example 2, page 7; SEQ ID NO: 1 in the sequence listing of that reference) as well as insertional mutagenesis to inactivate the poxB gene to produce L-lysine.

9. Hanke (U.S. Patent No. 6465238, claims priority to provisional application 60/150017 filed on 8/20/1999) discloses a method for producing L-lysine wherein Corynebacteria has been modified to increase NADPH, wherein said increase in NADPH is obtained by increasing the carbon flux through the oxidative branch of the pentose phosphate pathway (columns 2-5). Hanke et al. also teach that increasing the carbon flux through the oxidative branch of the pentose phosphate pathway can be achieved by increasing the intracellular amounts of the enzymes involved in this pathway including 6-phosphogluconate dehydrogenase (column 5, lines 1-10).

Conclusion

10. No claim is in condition for allowance.

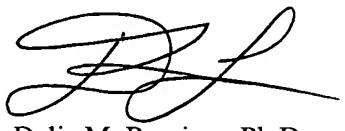
11. The cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available

on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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DR
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